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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/711,162	08/28/2004	Vladimir Khripach		5161

7590 10/03/2005

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EXAMINER
HARLE, JENNIFER I

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/711,162	KHRIPACH ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 are pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The breadth of the claims and nature of the invention: The claims are broad in that they are drawn to inhibition or treatment of HIV infection and the prophylaxis or therapy of AIDS and related diseases and pharmaceuticals for said treatment and prophylaxis. Treatment is an in vivo use, inhibition/prophylaxis is interpreted as the ability to halt HIV, AIDS and its related diseases, which would include the spread. The related diseases are almost unquantifiable because the related diseases of AIDS result when the immune system is compromises and could be any disease that would come about due to a comprised immune system, including something as simple as the common cold and ranging to the various cancers.

The level of predictability in the art and the amount of direction provided by the inventors: The language of the claims is not strictly limited to *in vitro* treatments and encompass treating infected patients and as such do not have support in the specification. There is insufficient disclosure to reasonably predict that the methods and compositions of the instant

specification would inhibit or treat HIV infection or be able totreat or prevent ADIS and their related diseases *in vivo* whether as a pharmaceutical/food supplement or as a vaginal tract protecting HIV-inhibiting composition. This is merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity. Applicant has only shown cell culture data, not treating infected patients or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate that there is no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the *in vitro* assays, the agent is in contact with cells during the entire exposure period. This is not the case *in vivo* where exposure to the target site may be delayed or inadequate. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation or immunological activation. In addition, the composition may not reach the target cells because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells, and tissues where the composition has no effect and/or a large enough local concentration may not be established. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat infected patients. One is only left with speculation and an invitation to experiment. Therefore, the claimed invention lacks an enabling disclosure.

Applicants have not even provided any animal modeling. Furthermore, the specification is not enabled for an *in vitro* system which models *in vivo* conditions. The extant of infection is not

clearly elucidated in the art and thus, one would not know how to mimic it. Additionally, there are other influences *in vivo* that are not in an *in vitro* system. The cells of a living body do not continuously grow and divide at the rate seen in a cell culture system. Further, the model does not include the complex interaction of numerous cell types and chemical signals as well as activation of T-cells by antigens. All of these would influence the behavior of the course of *in vivo* infection.

It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation. Further, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al., clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection. The failure of all immune-system-boosting therapies for treating AIDS is further discussed by Fox (V). Thus, it is clear from the

evidence of Fahey et al. and Fox, that the ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success. Applicants have not provided any convincing evidence that their immunoconjugate is indeed useful **for an anti-HIV treatment or for a binding assay** and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure. Moreover, Applicants' own data shows that EBI, even in a cell line does not eradicate HIV infected cells, the language states that it has an ability to protect against but no statistical data is provided about living vs. dead cells. The only quote we have is that "[t]hose probes were estimated as positive ones, where the amount of the living cells was 75% higher that in EBI-untreated virus control, which implies that there were living cells in the EBI treated assays. The examiner notes that cell line tests can lead one to potential candidates for further testing but cell lines in and of themselves are still just a step in a chain to provide an enabling disclosure. Thus, HIV and AIDS would remain a problem as it would continue to replicate and mutate in vivo and as we have no data on an in vivo system, there is no way to correlate whether this would ever work or at what dosage would be required.

Fahey et al. "Status of immune-based therapies in HIV infection and AIDS", Clinical and Experimental Immunology, Vol. 88 (1992), pages 1-5.

Fox "No winners against AIDS", *Bio/Technology*, Vol. 12 (Feb. 1994), pg 128.

Additionally, as to the vaginal tract protecting HIV-inhibiting compositions, there are additional enablement problems. While topical microbicides represent a potential new strategy for reduction of HIV transmission, Applicants have failed to provide any enabling disclosure.

According to Lard-Whiteford, both non-clinical and clinical developments of microbiocides present unique challenges and non-clinical development of a potential microbicide encompasses studies in several areas, including microbiology, pharmacology/toxicology, and chemistry/manufacturing, and controls – with the main purpose of these studies to ensure that the estimated risk/benefit profile of a novel pharmaceutical (i.e. EBI) is reasonable for the proposed indication before it is introduced into humans in clinical trials. Lard-Whiteford, et al., Recommendations for the Nonclincial Development of Topical Microbicides for Prevention of HIV Transmission: An Update, J. Acuir. Immune Defic. Syndr., May 1, 2004, Vol. 36, No. 1, pp. 541-552, 541. A microbiocide must have a high level of in vitro activity, in the presence of semen, against cell-free and cell-associated HIV-1, and multiple HIV-1 strains/subtype, low cytotoxicity in vitro, no or low activity against vaginal lactobacilli in vitro an no effect on vaginal pH, no or low irritation to vagina and nonimmunotoxic, nongenotoxic, no adverse effects on reproductive health in animals, noncarcinogenic, formulation suitable for vaginal application in an effective, appealing and efficient delivery system, stable under the conditions likely to be encountered, compatible with condoms and other physical barrier methods and desirable characterisitics include no or low systemic absorption in animals (noting that although systemic absorption does not rule out use of a compound as a microbicide, it does make nonclinical development more complicated), active in animal model systems, high genetic threshold to the development of resistance, active against other STI pathogens in vitro and/or in animal models, acceptable color, odor, consistency, and taste, good potential for industrial production at an economic cost, easy to use, possible for rectal application. Id at. 550.As set forth above, there is no real determination of anti-viral activity (we have no idea about the cell lines used or the exact

level of in vitro activity and no evidence of activity in the presence of semen or against multiple HIV-1 strains/subtypes), there is no evidence provided about its activity against vaginal lactobacilli in vitro or its effect on vaginal pH, no evidence about how it effects the vaginal or its immunotoxicity, genotoxicty, whether there are any effects on reproductive health in animals, if at any dosages it could be carcinogenic, while they state that it can be made in a vaginal formulation there is no guidance on how to make it in an effective, appealing and efficient delivery system (other than it is well known in the art and to see Remington's), no evidence is provided that is will remain stable under the conditions likely to be encountered or that it is compatible with condoms and other physical barrier methods. Then taking into account the desirable characteristics the only evidence provided is that it is active against HSV in vitro and Applicants have not even shown that there is a good potential for industrial production of a pharmaceutical grade at an economic cost. Thus, Applicants have failed to set forth an enabling disclosure for vaginal tract protecting HIV-inhibiting compositions containing EBI.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 5-6 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As per claim 1, the phrase "a plant hormone of structural formula I belonging to the brassinosteroid series is confusing because there is no structural formula 1" and there does not appear to be any reference in the specification to "brassinosteroid series".

As per claim 2, the phrase "related diseases" is vague and indefinite because it is unclear what diseases Applicants' are trying to encompass. See the rationale set forth above.

As per claims 3 and 6, the phrase "the aims of the present invention" is vague and indefinite because it is unclear to what aims are being referred. The examiner has interpreted this phrase to mean inhibition or treatment of HIV infections and prevention or treatment of AIDS and related diseases.

Regarding claim 5, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 3 and 5-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4 of copending Application No. 10/710,613. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method teaches the administration of a pharmaceutical/food product in the effective amount taught in the specification, and it would

have been obvious to a skilled artisan to have made the pharmaceutical given that it was being administered, in the well established forms of tablets, capsules, powders, solutions, etc. or incorporating a food product into a food material.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Franek, et al., 24-Epibrassinolide at Subnanomolar Concentrations modulates Growth and production Characteristics of a Mouse Hybridoma, Collect. Czech. Chem. Commun., 2003, Vol. 68, pp. 2190-2199, discloses a pharmaceutical composition used on a cell line, however, it is not in a therapeutically effective amount as described in the specification and that 24-epibrassinolide has equivalent biological activity to brassinolide.

Khripach, et al, Brassinosteroids A New Class of Plan Hormones, Practical Applications and Toxicology, Toxicology of BS, Academic Press, 1999, pp. 345-346, discloses that brassinsteroids were mainly concentrated in plant pollens and they were used in folk medicine for biostimulation and also form the basis for the production of some anti-inflammatory and metabolism stimulative medicines which are especially recommended for children and elderly people with chronic infections, however, no amounts are taught and 24-epbrassinolide is not taught.

Chinese Patent No. 1491653A, Xian, et al., April 24, 2004, discloses the pharmaceutical use of brassinolide to reverse multi-drug resistance of cancer cells. However, it does not specify any amount nor does it teach any alternatives, i.e. 24-epibrassinolide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

September 29, 2005